I. REMARKS

A. Status of the Claims

Claims 1-2, 5-16, 18-20, 25-30, 35-36 and 49-53 are pending in the Application.

Claims 3-4, 17, 21, 23, 31-34 and 37-48 were previously cancelled. Claims 17, 22, and 24 are cancelled herein.

Independent Claims 1, 14 and 18-20 are amended herein to more clearly show the sequential steps of the claimed methods. It is believed that these amendments are a matter of form and are not substantive.

Amendments were made to Claims 1, 14, 16, 18 and 20 to make it clear that the liquid solution contains the biologically compatible polymer dissolved in the liquid and it is the liquid solution that is sprayed from the outlet. As discussed in paragraph **[0018]** and **[0033]** to **[0040]**, the liquid solution is sprayed using an electrohydrodynamic means to produce charged fibers which are attracted to a grounded surface.

Amendments were made to Claims 1, 14, 16, 18 and 20 to require that the biologically compatible polymers used in the invention are not electrically conductive. This amendment is made in response to the observation made by Examiner at page 11, lines 1-5 of the Office Action dated May 12, 2009.

Claim 24 is cancelled herein and New Claim 54 is added to capture the subject matter of Claim 24 when a polymer melt is used in the claimed method. Claim 54 is directed to a specific embodiment of the invention where the polymer is a "melt", that is, the polymer is heated until it becomes a liquid (usually somewhat viscous) and then sprayed from the outlet. Support for this amendment is found in claim 24 as originally filed and in paragraph **[0009]**.

Applicant's attorney has made a good faith effort to ensure that the amendments to the claims have been properly "marked" using the currently recommended format. Any errors which may have occurred are inadvertent and Applicant's attorney will make every effort to correct any such non-substantive inadvertent errors.

B. Petition for Extension of Time

Accompanying this Response is a Petition for Extension of Time (PTO/SB/22) for a 1-month extension as well as the required fee.

II. CLAIM OBJECTIONS

Examiner objects to Claim 4 as being of improper dependent form for failing to further limit the subject matter of the previous claim. Claim 4 is cancelled herein, thus, obviating Examiner's objection to Claim 4 on this basis.

Examiner objects to Claims 16, 19, 50, and 51 for the inconsistent use of "fiber" for "fibre". Applicants have corrected the term fibre in these claims removing the inconsistency.

III. REJECTION UNDER 35 USC §112, 2ND PARAGRAPH REJECTION

A. Paragraph One Rejections.

1. Claim 14 is amended to require a gap size of from 10 to 500 microns which is a range supported in the specification as a whole and in particular at paragraph **[0009]**. It is believed that this amendment overcomes Examiner's rejection of claim 14 on this basis.

2. Claim 22 is cancelled herein and thus, the rejection of claim 22 under Section 112, 1st Paragraph is overcome.

B. Paragraph Two Rejections.

1. Examiner alleges Claims 1, 18, and 20 are indefinite because the recitation "said biologically compatible polymer liquid" lacks antecedent basis. Applicants have amended these claims to make it clear that the liquid solution contains a biologically compatible polymer dissolved in the liquid solution.

2. Claim 3 is rejected because the stated range of the fiber particle diameter is not narrower than the claim from which Claim 3 depends. Claim 3 is cancelled herein and it is believed that the rejection of Claim 3 on this ground has been obviated.

3. The punctuation in claim 10 is corrected to remove the ":" after the term polylactide in line 2 of the claim. It is believed that this amendment overcomes Examiner's rejection on this basis.

4. Claim 14 is rejected as containing improper grammar and improper punctuation. It is believed that Claim 14 as amended fully meets the requirement of Section 112, 2nd paragraph and Examiner's rejection of Claim 14 has been overcome.

5. Examiner contends that Claim 18 is indefinite since the recitation, "... resulting cells have a morphology resembling nerve cells" is confusing. This language is fully supported by Example 3, **Fig. 11** and **12** and paragraphs **[0113]** – **[0115]** of the specification and in particular, in paragraph **[0115].** It is respectfully asserted that the rejection is in error and should be withdrawn.

6. As discussed above, Claim 22 is cancelled herein rendering Examiner's Section 112, 2nd paragraph rejection moot.

IV. Rejection Under 35 U.S.C §103(a)

A. The Section 103 Rejections

1. The first Rejection

Claims 1-16, 18, 20, 22, 24-28, 35-36, and 49-53 are rejected under 35 USC §103(a) as being unpatentable over Shastri *et al.* (WO/97/16545) in view of Coffee *et al.* (WO 98/03267), Sussman *et al.* (US 5,266,476), and Leong *et al* (US 5,686,091).

2. The Second Rejection

Claims 1-16, 18-20, 22, 24-30, 35-36, and 49-53 are rejected under 35 USC §103(a) as being unpatentable over Shastri *et al.* (WO/97/16545) in view of Coffee *et al.* (WO 98/03267), Sussman *et al.* (US 5,266,476), and Leong *et al* (US 5,686,091) and further in view of Smith et al. (WO 01/27365) and Simpson et al. (WO 02/40242)..

In connection with the cited references except Shastri and Coffee, Examiner states the following:

- "...Sussman is used solely to teach suitable fibre diameters."
- " ... Leong is provided solely to teach the criticality of the pore size of the scaffold."
- "... Smith is used solely to render obvious the use of polycaprolactone."
- "...Simpson ... is used solely for its teachings that electroprocessing may be used to expose a liquid formulation to an electric field to cause the liquid to break up into droplets or to form at least one fibre."

Based on Examiner's explicit characterization of the references described in this paragraph, it appears that by Examiner's own admission, if the Shastri and Coffee references taken together do not render obvious Applicant's claimed invention, then Sussman, Leong, Smith and Simpson taken together fail to do.

B. The Issue

The question to be decided is whether the teachings of Shastri and Coffee taken together render Applicant's presently claimed invention obvious within the meaning of 35 USC §103(a)?

C. Analysis

The Shastri reference broadly teaches methods for stimulating nerve cells, and more specifically, to methods for promoting attachment, proliferation, and differentiation of nerve cells by electrical stimulation of the cells on electrically conducting polymers.

The electrically conducting polymers described as being preferred for use in the methods of the Shastri invention are polyanilines, polypyrroles, and polythiophenes as well as derivatives of these polymers (p.6, lines 15-16). Polypyrrole is the especially preferred for use in the methods of Shastri.

Shastri describes *in vitro* and *in vivo* use of the electrically conducting polymers (p. 18, lines 10-30, pp. 19 & 20 all, and p.21, lines 1-24). When *in vitro* growth of nerve cells is carried out, the cells are cultured by disposing the cells on thin films of electrically conducting polymers and then stimulating the polymer with an applied voltage sufficient to promote *in vitro* proliferation or regeneration. Example 3 of Shastri provides details of the *in vitro* method and **Fig 3** provides details of the device used.

Shastri also describes the preparation of electrically conducting polymers laminated to other polymeric materials. The "other polymeric materials" include biocompatible polymers which are not biodegradable and biocompatible polymers which are biodegradable; Table I provides a listing of these other polymers.

Table I

Biocompatible but Non-biodegradable		Biocompatible and Biodegradable	
Poly(styrene)	Poly(esters)	Poly(anhydrides)	Poly(hydroxy acids)
polyurethanes	polyureas	Poly(lactic acid)	Poly(lactic-co-glycolide)
Poly(ethylene vinyl acetate)	Poly(propylene)	Poly(orthoesters)	Poly(propylfumarate)
Poly(methacrylate)	Poly(ethylene)	proteins	Polymerized proteins e.g. collagen
Poly(ethylene oxide)	glass	polysaccharides	heparin
polysilicates	Poly(carbonates)		
teflon	Fluorocarbons		
nylon	Silicon rubber		

Shastri uses the laminates to make a matrix for implantation in patients to form new tissue. The reference teaches that the matrix should be a pliable, non-toxic, porous template for vascular ingrowth. The pores should allow vascular ingrowth and the seeding of cells without damage to the cells or patient. Shastri clearly teaches that the electrically conducting polymer is essential for successful growth of new cells by the implant. Growth of cells on the non-electrically conducting polymer, poly(lactic acid) ("PLA") was found to be poor (p.25, lines 21-24) and also, PLA induced more inflammation than did the electrically conducting polypyrrole (p. 28, lines 15-19).

Claim 18 of Applicants is directed toward a method wherein the gap size and fiber diameter are controlled so that when human bone marrow cells are applied to the 3-dimensional fiber scaffold and allowed to grow, cells having the morphology of nerve cells are produced. This very surprising result is not taught or suggested by the Shastri reference.

Examiner admits that Shastri does not expressly disclose that the polymer on which the cells are attached is a fibre scaffold created by supplying a liquid comprising the biologically compatible polymer to a liquid outlet in the vicinity of a surface and subjecting the liquid issuing form the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits on the surface. In order to fill this lack of disclosure Examiner cites the Coffee reference.

Coffee teaches the preparation of polymer fibre mats which may be used as a dressing in wound healing. The fibres are prepared using electrohydrodynamic means which generally requires the polymer to be dissolved in a carrier liquid. The carrier liquid containing the dissolved polymer is sprayed (aerosolized) by means of the application of voltage to either the EHD device nozzle or the liquid itself. The charge placed on the liquid (or nozzle) is sufficient to overcome the surface tension of the liquid and as a result droplets, or fibres or fibre fragments are formed which carry a charge but when the fibres deposit on the grounded substrate (surface) the charge is discharged. The resulting fibre mat is electrically neutral.

The polymers disclosed by Shastri are required to be electrically conducting polymers. This is necessary because growth and differentiation of nerve cells is achieved by electrical stimulation of the cells deposited on electrically conducting polymers. In the methods disclosed by Applicant, polymer fibers are formed using electrohydrodynamic means and thus, have an electric charge once they are formed. However, as soon as the fibers deposit on the target surface the charge is dissipated. The polymer scaffolds formed by Applicant's method are not charged nor are they electrically conductive. Surprisingly, Applicant is able to obtain cell growth and differentiation by choice of a specific fiber diameter and space (gap) between adjacent fibers (the gap size).

None of the conductive polymers described by Shastri are used in the inventions of Applicant. Although Shastri (Col 8, lines 39-53) teaches that the electrically conducting polymers described therein (See Col's 3-6) may be laminated onto or blended with other biocompatible, non-conductive polymers, there is nothing in the reference that teaches one skilled in this art that non-conductive polymers when used alone, may be used to grow nerve cells.

The Coffee reference describes the use of electrohydrodynamic ("EHD") means to produce fibers or fiber fragments or segments that are solid, or partially solid and which are sprayed on a wound or burn on a human or animal. Fibres having diameters in the range of from 10 nm to above 100 μm and typically from 10^2 to 10^4 nm may be produced. The fibers may be bioresorbable or biodegradable and may have a biologically active agent e.g., pharmaceutical or DNA or growth factor applied to the surface of the fibers or the active biological agent may be encapsulated by the fibers.

Unlike Applicant's claimed methods, there is no disclosure in the Coffee reference that suggests that the ratio of the diameter of an individual fiber to the size of the space between individual fibers (gap) is critical to the invention of Coffee much less, to the growth of cells *in vivo*. Examiner admits that this is true at page 6, second paragraph of the Office Action where it is stated that the Shastri and Coffee references "... do not expressly disclose selecting a fiber diameter and a size of the gaps between the fiber portions that facilitate a cell process."

There is nothing in the teachings of either the Shastri reference or the Coffee reference which suggests mammalian cell growth may be facilitated by use of a polymer fiber scaffold where the polymer fiber diameter and the space between adjacent polymer fibers are controlled.

V. ARGUMENTS

What does the combination of Shastri and Coffee suggest to one skilled in the art? Shastri explicitly teaches that an electrically conductive polymer is required to be used as the substrate (surface) for *in vitro* and *in vivo* cell growth. Shastri also teaches that the electrically conducting polymer (e.g. polypyrrole) may be laminated to a non-conducting polymer to form structures that may be formed into e.g., suturable disks or tubes which may be implanted in a patient in order to grow cells *in vivo*.

Coffee teaches the preparation of polymer fibre mats which may be used as a dressing in wound healing. The fibres are prepared using electrohydrodynamic means which generally requires the polymer to be dissolved in a carrier liquid and then the carrier liquid containing the polymer is sprayed (aerosolized) by means of the application of a voltage to either the nozzle or the liquid itself in the vicinity of a grounded substrate (surface). When the liquid leaves the

nozzle the charge is sufficient to overcome the surface tension of the liquid and as a result droplets, or fibres or fibre fragments are formed which carry a charge but when the fibres deposit on the substrate the charge is discharged. The resulting fibre mat is electrically neutral.

The combination of Shastri and Coffee might teach a skilled artisan the following:

- Shastri might be led to use polyvinyl alcohol or New Skin disclosed by Coffee as a laminating protein.
- Coffee might be led to prepare wound dressings using electret polymers;
- Shastri might be motivated to use Coffee's EHD method to prepare various electrically conductive polymer films for use in the methods of Shastri's invention.

What the references would not do is lead the skilled artisan to use the EHD method of Coffee to prepare non-conductive polymer substrates and to use these non-conductive polymer substrates to grow cells *in vitro* or *in vivo*. Shastri specifically teaches that growth of cells on the electrically conductive poly(pyrrole)/poly(styrene sulfonate) film was superior to growth of cells on poly(lactic acid) film which was "poor".

One skilled in this art is taught by Shastri that one must use electrically conductive polymers to obtain satisfactory cell growth. Applicants claimed method is directed to methods where the biologically compatible polymer used in the methods is not an electrically conductive polymer.

Assuming one skilled in this art combined the teachings of Shastri and Coffee, it is respectfully contended that whatever the invention resulting from the combination it would contain as an essential feature an electrically conductive polymer. Applicant's claimed method does not require the use of an electrically conducting polymer. To the contrary, Applicant's claims as presently amended, limits the polymers used in the method to electrically non-conducting polymers. There is no logical reason that the skilled artisan would have used the non-conductive polymer fibre scaffold disclosed by Coffee in the invention of Shastri which requires the use of electrically conductive polymers for adequate cell growth.

In reliance on Examiner's representation of Examiner's use of the Sussman, Leong, Simpson and Smith references described above, Applicant has not thoroughly analyzed the contents of these references. However, Applicant did thoroughly analyze the disclosures of the Sussman, Leong, Simpson and Smith references and the differences between the references and Applicant's claimed methods in the Response dated January 28, 2009. The analysis is not repeated herein but is incorporated into this discussion.

It is respectfully asserted that based on the analysis presented herein, Applicant has demonstrated that none of the references taken individually or collectively render Applicant's claimed invention obvious within the meaning of Section 103(a).

VI. CONCLUSION

Based on the amendments and arguments made herein, it is respectfully asserted that Examiner's rejections have been overcome and that this application is in condition for allowance. Examiner is respectfully requested to withdraw all rejections and to issue a Notice of Allowance. If there are any questions regarding these amendments and remarks, Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Date: September 10, 2009

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